REMARKS

Claims 21-40 were pending in the present application.

By this Amendment, claims 21-40 have been amended.

Support for amendments appears in the previously presented claims and the specification. For examples, support for amendments to claim 21 appears on, e.g., page 4, line 25, where shows "about 2-9 nm in diameter." Support for amendments to claim 24 appears on, e.g., page 46, lines 6, 16, and FIG. 1, where shows "5-thio-pentan-1-ol" (i.e., 5-thiopentyl-) as a linker. Support for amendments to claims 25 and 27 appears on, e.g., page 5, lines 16, 25, and page 19, lines 20-24, where show the target comprise a cell, the target comprises a bacteria, and mannose-nanoparticles binding to the pathogen bacteria in a subject, respectively. Support for amendments to claim 30 appears on, e.g., page 3, line 33.

No new matter has been added. Applicant respectfully requests that the amendments be entered.

Applicant through her attorney on the record and identified below appreciates the Examiner's careful review of the present application.

The following remarks herein are considered to be responsive thereto.

Claim Rejections – 35 USC § 112 Second Paragraph

Claims **26**, **36** and **40** were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that claims **26** and **36** recite "Shiga-like toxin," and it is unclear how like or unlike the toxin is to Shiga. It further states that claim **40** recite "the lectin," for which there is insufficient antecedent basis.

Applicant respectfully submits that the amended claims **26** and **36** do not recite "Shiga-like toxin," and amended claim **40** do not recite "the lectin."

It is respectfully requested that the rejections be withdrawn.

Claim Rejections – 35 U.S.C. §102(a)

The Examiner rejected Claims **21-25, 29, 30, 34, 35, 37** and **38** under 35 U.S.C. §102(a) as being anticipated by Lin et al. (JACS 2002, 124, 3508-3509).

In response, Applicant has submitted herewith Rule 131 Declarations, establishing that the article is describing Applicant's own work.

MPEP §2132.01 provides that where the applicant is one of the co-authors of a publication cited against his application, the rejection can be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

The authors of the article Lin et al. are **Lin, Chun-Cheng**; **Chen, Chia-Chu; Wu, Yi-Chun** and 4 other co-authors. The applicants of the present invention are **Lin, Chun-Cheng**; **Chen, Chia-Chu; Wu, Yi-Chun**. It is clear that the authors of the article Lin et al. were associated with Applicants (i.e., **Lin, Chun-Cheng**; **Chen, Chia-Chu; Wu, Yi-Chun**) and learned of Applicant's invention from the present inventors.

Further, enclosed herewith is a declaration under 37 C.F.R. §1.131 showing that the authors of Lin et al. learned of Applicant's present invention from the present inventors and published the research paper Lin et al. In view of the above comments, reconsideration and withdrawal of the rejection of claims **21-25, 29, 30, 34, 35, 37** and **38** are respectfully requested.

Claim Rejections – 35 U.S.C. §102(b)

The Examiner rejected claims **21-23**, **31**, **33**, **35** and **38** under 35 U.S.C. §102(**b**) as being anticipated by de la Fuente et al. (Angew Chem 2001, 113(12), 2317-2321).

Legal Standard

MPEP § 2131.01 states that "**[t]o anticipate a claim, the reference must teach every element of the claim**." [emphasis added.]

de la Fuente et al. does not anticipate amended claims **21-23**, **31**, **33**, **35** and **38** for the following reasons.

de la Fuente et al. teaches making glyconanoparticles for use as 3D models to mimic glycosphingolipid (GSL) clustering at the cell surface to investigate carbohydrate-carbohydrate interactions in solution (Page 2319, Column 1, last paragraph). de la Fuente et al. teaches selection of two biologically significant oligosaccharides, the **disaccharide lactose** and the **trisaccharide Le^x** and two linkers 11-thioacetate-3, 6, 9-trioxa-**undecanol** and 11-thioacetate **undecanol**. The glyconanoparticles taught by de la Fuente et al. is **1.8 nm** in diameter with **a ratio of 63 (lactose-1), 70 (lactose-2), and 97 (Lex-3) molecules per 201 gold atoms** (Page 2319, Column 1, first paragraph).

Claim **21** requires "the saccharide-conjugated nanoparticle has an average diameter of about 2-9 nm," which is not taught or suggested by de la Fuente et al.

Claim **22**, depending on claim **21**, further requires, among others, "the plurality of saccharide molecules are selected from the group consisting of a monosaccharide and a Pk antigen," which is not taught or suggested by de la Fuente et al.

Claim **23** requires, among others, the following elements: "(1) the saccharide-conjugated nanoparticle has an average diameter of about 2-9 nm; and (2) the plurality of saccharide

molecules comprises at least 150 molecules," neither of which is taught or suggested by de la Fuente et al.

Claim **31**, directed to a composition, requires, among others, the following elements: "the monosaccharide is selected from the group consisting of mannose, galactose, and glucose," neither of which is taught or suggested by de la Fuente et al.

Claim **33** requires "(1) 5-thio-pentan-1-ol, (2) the plurality of saccharide molecules are at least 150 molecules, and (3) a pathogen, bound to the saccharide-conjugated nanoparticle," none of which is taught or suggested by de la Fuente et al.

Claim **35** requires "the plurality of saccharide molecules are selected from the group consisting of a monosaccharide and a Pk antigen," neither of which is taught or suggested by de la Fuente et al.

Claim **38** depends on claim **35** and further requires "a pathogen bound to the nanoparticle," which is not taught or suggested by de la Fuente et al.

Thus, de la Fuente et al. does not anticipate claims **21-23**, **31**, **33**, **35** and **38**.

It is respectfully requested that the rejections be withdrawn.

Claim Rejections – 35 U.S.C. §103

Claims **21-40** were rejected under 35 U.S.C. §103(a) as being unpatentable over de la Fuente et al. (Angew Chem 2001, 113(12), 2317-2321 in view of Lin et al. (JACS 2002, 124, 3508-3509) and Beuhamou (Colloidal Gold 1989 Academic Press, Inc. Sand Diego, CA chapter 4, pages 95-141) and Sandvig et al. (The Journal of Cell Biology 1989, 108, 1331-1343).

Legal Standard for Obviousness Rejection

The legal standard for establishing a prima facie case of obviousness requires that the references "teach or suggest all the claim limitations." *See* MPEP §2143. (Emphasis added.)

Claim **21** requires "the saccharide-conjugated nanoparticle has an average diameter of about 2-9 nm,"

Claim **22**, depending on claim **21**, further requires, among others, "the plurality of saccharide molecules are selected from the group consisting of a monosaccharide and a Pk antigen."

Claim **23** requires, among others, the following elements: "(1) the saccharide-conjugated nanoparticle has an average diameter of about 2-9 nm; and (2) the plurality of saccharide molecules comprises at least 150 molecules.

Claims **24**, **27** and **39**, depending on claim **21**, **25** and **38**, respectively, each requires, among others, "a subject infected with the pathogen."

Claim **25**, directed to a composition, requires, among others, "a pathogen, bound to the saccharide-conjugated nanoparticle."

Claim **26**, depending on claim **25**, further requires "the pathogen is selected from the group consisting of bacteria, viruses, mycoplasma and fungi."

Claim **28**, depending on claim **25**, further requires "the plurality of saccharide molecules are selected from the group consisting of a monosaccharide and a Pk antigen."

Claim **29**, depending on claim **25**, further requires "5-thio-pentan-1-ol."

Claim **30** and **36**, depending on claims **25** and **35**, respectively, each further requires "the plurality of saccharide molecules comprise at least 150 molecules."

Claim **31**, directed to a composition, requires, among others, the following element: "the monosaccharide is selected from the group consisting of mannose, galactose, and glucose."

Claim **32**, depending on claim **25**, further requires "the plurality of saccharide molecules are Pk antigen."

Claim **33** requires "(1) 5-thio-pentan-1-ol, (2) the plurality of saccharide molecules comprise at least 150 molecules, and (3) a pathogen, bound to the saccharide-conjugated nanoparticle."

Claim **34**, depending on claim **29**, further requires "(1) 5-thio-pentan-1-ol, (2) the plurality of saccharide molecules are selected from a monosaccharide and a Pk antigen, and (3) a pathogen, bound to the saccharide-conjugated nanoparticle."

Claim **35** requires "the plurality of saccharide molecules are selected from the group consisting of a monosaccharide and a Pk antigen

Claims **37** and **40**, depending on claims **35** and **38**, respectively, each further requires "the monosaccaride is selected from the group consisting of mannose, galactose and glucose."

Claim **38**, depending on claim **35**, further requires "a pathogen, bound to the nanoparticle."

As discussed above, Lin et al. has been removed from prior art because it cannot be a valid reference. This leaves 3 references to be addressed as follows.

The teaching and the failures of the primary reference de la Fuente et al. have been mostly discussed above.

In summary, the primary reference de la Fuente et al. fails to teach the following elements (A) to (J):

(A) "5-thio-pentan-1-ol," which is required by claims **24**, **29** and **33**.

(B) "the plurality of saccharide molecules are selected from the group consisting of a monosaccharide, and a Pk antigen," which is required by claims **22**, **28**, **34** and **35**.

(C) "a subject infected with the pathogen," which is required by claims **27** and **39**.

(D) "a pathogen, bound to the saccharide-conjugated nanoparticle," which is required by claims **25**, **33**, and **38**.

(E) "the pathogen is selected from the group consisting of bacteria, viruses, mycoplasma and fungi," which is required by claim **26**.

(F) "the saccharide molecules comprise at least 150 molecules." which is required by claims **30**, **33** and **36**.

(G) "the monosaccharide is selected from the group consisting of mannose, galactose, and glucose," which is required by claims **31**, **37** and **40**.

(H) "the plurality of saccharide molecules are Pk antigen," which is required by claim **32**.

The failures of the primary reference de la Fuente et al. are not remedied by the combination of Benhamou and Sandvig et al.

Nether Benhamou nor Sandvig et al. teaches or suggests the aforementioned elements (A) to (H). Benhamou teaches lectin-gold complexes, in which colloidal gold binds lectins by noncovalent electrostatic adsorption (Page 96, first paragraph). Benhamous teaches that lectins are recognized as a class of proteins or glycoproteins having binding sites for specific sugars (Page 104, first paragraph). Benhamou teaches incubation of the tissue sections with lectin-gold complexes for the localization of intracellular lectin receptors (page 109, paragraphs 2-3).

Sandvig et al. teaches endocytosis is involved in the transport to the cytosol of Shiga toxin (Abstract).

Because the references when combined do not teach or suggest all the claimed elements, claims **21-40** are nonobivous over the cited references.

Moreover, the cited references in combination do not align with the claimed invention in principles of operation.

The gold glyconanoparticles of de la Fuente et al. are **structured and operated differently** from the clamed invention. The invention is structured to operate as a tool for labeling cellular proteins that bind specifically to the conjugated saccharides.

The principles of operation in de la Fuente et al. are presentation of a "three-dimensional (3D) model system for the study of carbohydrate interactions." The 3D model gold glyconanoparticles designed by de la Fuente et al. are to solve the challenges faced in studying "a hemophilic carbohydrate-carbohydrate interaction between the Lewis^x antigen," and "a heterotropoic interaction between glycosphingolipid patches of GM3 and Gg3 involved in metasstais of melanoma cells." *See* page 2318, first paragraph.

By the nature of their structural design, the gold glyconanoparticles in de la Fuente et al. each have necessary structural components to result in Lewis^x antigen interactions and/or to allow potential interactions between glycosphingolipid (GSL) microdomains.

Fuente's gold glyconanoparticles were intended to mimic glycosphingolipid (GSL) microdomains, the lipid chain is thus necessary. The gold glyconanoparticles therein contain undecanol (11 carbons) as one part of his glyconanoparticle to mimic cell surface lipid bilayer. Their system "consists of gold nanoclusters functionalized with neoglycoconjugates of biologically significant **oligosaccharides**." (page 2318, column 1, first paragraph) Their gold

glyconanoparticles comprises either the disaccharide lactose or the trisaccharide Le^x so that the Le^x-Au was able to show self-recognition and self-aggregation so as to mimic the "hemophilic carbohydrate-carbohydrate interaction between the $Lewis^x$ antigen," which "seems to be responsible for morula compaction." (page 2318, first paragraph; and page 2320, first paragraph.)

One of ordinary skill in the art at the time the invention was filed would not have been motivated to modify the oligosaccharides lactose and Le^x of de la Fuente et al. with Applicant's monosaccharides such as mannose, galactose and glucose, and/or Pk antigen because such a modification would not align with the principles of operation in prior art.

Furthermore, one of ordinary skill in the art at the time the invention was filed would not have been motivated to modify the two linkers 11-thioacetate-3, 6, 9-trioxa-undecanol and 11-thioacetate undecanol (11 carbons) of de la Fuente et al. with Applicant's linker 5-thio-pentan-1-ol (5 carbons) because such a modification would deviate from the prior at principles of operation, i.e., to mimic glycosphingolipid (GSL) clustering and study potential interactions between glycosphingolipid (GSL) microdomains. *See* page 2318, first paragraph; page 2319, column 1, last paragraph.

Benhamou's lectin-gold complexes are **structured and operated differently** from the clamed invention as well. As discussed above, theirs have no chemical compound as a linker and have no saccharides conjugated to the gold particles. Theirs are for labeling intracellular lectin receptors, which are carbohydrates with specific binding affinities to lectins. Essentially, the principles of operation in their gold complexes are probing lectins-binding sites.

Sandvig et al. presents no glyconanoparticles. The teaching in Sandvig et al. is about endocytosis of Shiga toxin. The principles of operation therein have nothing to do with labeling cellular protein.

Applicant respectfully submits that an obviousness test requires comparing the claimed invention as a whole to a prior art reference. Claimed limitations are not puzzle pieces to be matched to atomized prior art suggestions, and thus examined out of context. As with obviousness in combining prior art references, only if the prior art aligns with the claimed invention in principles of operation may a prior art reference be considered anticipatory.

When applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; nad

(D) Reasonable expectation of success.

Applicant further respectfully submits that while Patent Office classification of references and the cross-references in the official search notes of the class definitions are some evidence of "nonanalogy" or "analogy" respectively, the court has found "the similarities and differences in structure and function of the inventions to carry far greater weight." In re Ellis, 476 F.2d 1370, 1372, 177 USPQ 526, 527 (CCPA 1973).

If the proposed modification or combination of the prior art would change the principles of operation of the prior art invention being modified, then the teaching of the references are not

sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Applicant respectfully requests the Examiner reconsider the appropriateness of combining prior art references or specific features thereof, especially regarding the similarities in purpose ("nature of the problem"), function, and structure. Applicant considers the references are not appropriate to combine. Even if they were to be combined, the combination would not arrive at a saccharide-conjugated nanoparticle with the same or similar principles of operation as the claimed invention. The references would not add up to the claimed invention.

The inventors of this application have exercised diligent inventive efforts and discovered a composition that offers a tool for labeling cell surface proteins. To the best knowledge of the inventors, at the time the invention was made, there were only few publications about gold glyconanoparticles. (~1 or ~2 articles). The inventors were the first to discover gold nanoparticles for labeling cell surface proteins. The inventors were also the first to report that mannose-gold nanoparticle shows **stronger** interaction with bacterial FimH adhesion than **free mannose** (Sepcification, Table 4). The invention has been demonstrated as an efficient labeling probe in a biological system.

Accordingly, Applicant respectfully requests that the § 103 rejections be withdrawn.

No fee is due because Applicants paid the filing fee for 3 independent claims and 20 total claims, and as set forth above, per this Amendment, there are 20 claims pending including 3 independent claims.

Any amendments to the claims not specifically referred to herein as being included for the purpose of distinguishing the claims from cited references are included for the purpose of clarification, consistence and/or grammatical correction only.

It is thus believed that the application is in condition for allowance at least for the above reasons and such allowance is respectfully requested.

CONCLUSION

Applicant respectfully submits that the foregoing Amendment and Response place this application in condition for allowance. If the Examiner believes that there are any issues that can be resolved by a telephone conference to facilitate the prosecution of this application, or that there are any informalities that can be corrected by an Examiner's amendment, please call the undersigned at 650-557-4464.

Respectfully submitted,

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